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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,125	06/14/2001	Irwin Fridovich	1579-580	9188

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EXAMINER

HABTE, KAHSAY

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 12/07/2001

4

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/880,125

Applicant(s)

FRIDOVICH ET AL.

Examiner

Kahsay Habte, Ph. D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-27 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). ____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ 6) ☐ Other:

DETAILED ACTION

Specification

1. The disclosure is objected to because of the following informality: the figures that appear at the top of page 9 are of poor quality. Small numerals in the figures and what appear to be handwritten portions of the figures (such as "N" in the pyridinium rings) are obscured and, in some cases, illegible. Clean copies are required.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 10, 14, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Kaufmann *et al.* {Inorg. Chem. 34, (1995), 5073}. Kaufmann *et al.* teach the tetrakis(N-methyl-2-pyridinium)porphyrin of formula I and Zn(II), Cu(II), and Ni(II) complexes thereof of the claims. Furthermore, Kaufmann *et al.* teaches the mixture of atropisomers of claim 14, said mixture also being embraced by the language of claim 15 (see Figure 1 and the experimental section on page 5074).

3. Claims 1-5, and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Hambright {J. Inorg. Nucl. Chem. 39, (1997), 1102}. The cited reference teaches the

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tetrakis(N-methyl-2-pyridinium)porphyrin complexes of Mn(II) and Mn(III) of both formulae I and II of the claims (see experimental section on page 1102).

4. Claims 1-5, and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Hambright *et al.* {Porphyrin Chem. Adv., [Pap. Porphyrin Symp. (1979), Meeting Date 1977, 284-92]. The cited reference teaches the tetrakis(N-methyl-2-pyridinium)porphyrin complexes of Mn(II) and Mn(III) of both formulae I and II of the claims (see experimental section on page 284).

5. Claims 1-5 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Bütje *et al.* {Inorg. Chim. Acta, 167 (1990) 97-108} and Sari *et al.* {Biochemistry, 29, (1990), 4205-4215}. Bütje *et al.* teach the tetrakis(N-methyl-2-pyridinium)porphyrin and tetrakis(N-methyl-3-pyridinium)porphyrin complexes with Cu(II), Ni(II), and co(II) that correspond to formulae I and II of the instant claims (see Figure 1 on page 97, the experimental section on page 98, and Table 2 on page 99). Sari *et al.* teach the tetrakis(N-methyl-2-pyridinium)porphyrin and tetrakis(N-methyl-3-pyridinium)porphyrin and their complexes with Cu(II), Fe(II), and co(II) that correspond to formulae I and II of the instant claims (see Figure 1 on page 4206 and the "materials and Methods" section on page 4206-4208).

6. Claims 1-5, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Davila *et al.* {J. Chem. Soc. Chem. Commun., (1987), 525-527}. Davila *et al.* teach the

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tetrakis(N-methyl-3-pyridinium)porphyrin complex of Zn(II) corresponding to Formula II of the claims. The reference also teaches the tetrakis(N-ⁿhexyl-3-pyridinium)porphyrin complex of Zn(II) corresponding to Formula I of the claims when R = ⁿhexyl (see diagram on page 526).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention:

(a). Compounds of the instant invention are depicted in formulae I and II of the claims as discrete cations arising from the formal positive charges on the pyridinium nitrogen atoms. The written description, however, does not enable one skilled in the art how to make compounds that carry net positive charges. Compare to examples I – III of the written description that show how to make the neutral complexes as their PF₆⁻, p-toluenesulfonate, chloride, and iodine salts.

(b). Claims 1, 5, 16, 19, 21, and 23 are rejected because the specification, while enabling for the electron withdrawing groups for the electron withdrawing group P= Cl of

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formulae I and II, does not provide enablement for the scope of all conceivable electron withdrawing groups embraced by instant claim language.

In particular, claim 5 is rejected because it is not enabled for the electron withdrawing groups of nitrile, vinyl, nitro, and formyl. Even if applicants taught the parent nitrile (e.g. $-\text{CN}$), the scope of nitriles embraced by the claim language (i.e. a nitrile, a vinyl), etc.) would not be reasonably enabled. Applicants provide no guidance, suggestion, nor teaching as to how porphyrin compounds of formulae I or II are made when P = nitro, vinyl, or formyl. Note that the preparation of such derivatives does not appear to be known prior to applicants, effecting filing date. See the recent publication of Vodizinskii *et al.* (Russ. J. Org. Chem. 34(6) 1998, 882-885) that describe the synthesis of the first nitroporphyrin derivatives that contain heteroaryl *meso* substituents.

(c). Method claims 16-22 are rejected because they are not enabled for the scope of pathological conditions generally embraced by the claim language. A computer-assisted search did not yield references delineating any clear relationship between superoxide dismutase (or mimics thereof) and the treatment of the pathological conditions cited in the written description (page 15-18). However, inflammatory lung diseases and asthma in particular have been identified as treatable conditions by the antioxidant activity of superoxide dismutase as evidenced by Comhair *et al.* (Medline abstract) and Rosenfeld *et al.* (Medline abstract). Therefore, the intersection between one or more pathological conditions and the antioxidant mode of action relied upon herein appears to be not commensurate in scope with claim language and unknown for

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conditions other than those cited above. Where the utility is unusual, difficult to treat, or speculative, the examiner has authority to require a showing that the tests relied upon by applicants are reasonably predictive of *in vivo* efficacy by those skilled in the art. Note *In re Ruskin* 148 USPQ 221; *Ex parte Jovanovics* 211 USPQ 907. Also note MPEP 2164.05(a).

Additionally, compound actually tested, as evidenced by applicants' working examples and declaration of record, are limited to Mn TE-2-PyP (examples IX and XII) and Mn TM-2-PyP (example X). There is no reason to conclude that all of the compounds embraced by the instant claims would be equivalent to the two actually tested based upon comparable *in vivo* SOD activities (e.g. examples V and VI). See *In re Surrey* 151 USPQ 724 and MPEP 2164.03.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

(a). While applicants may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "P" in claims that contain formulae I and II (e.g., 1, 16, 19, 21, and 23) and all claims dependent thereon is used by the

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claims to mean "electron withdrawing group," while the art-recognized meaning is "phosphorus." Formulae I and II, therefore, each appear to indicate compounds containing eight exocyclic monovalent phosphorus substituents.

(b). Figures representing formulae I and II throughout the claims are of poor quality, thereby obscuring some features of the formulae, particularly those that appear to be written by hand. The examiner suggests that applicants submit claims with clean figures that are free of handwriting.

(c). The claims are vague and indefinite because it is not clear how the neutral – assuming the omission of counterions was inadvertent as addressed in the 112 first paragraph rejection – free base porphyrins of formula I and II can, *as drawn*, be "complexed with a metal" while retaining the N-H moieties as claim language embraces. Note that applicants' Figure 2, for example, indicates metalloporphyrins that lack said N-H moiety.

(d). The claims are vague and indefinite because compounds of formula I and II are represented as discrete cations, leaving open to speculation as to how said compounds achieve charge neutrality. The examiner suggests that inclusion of counterions as described throughout examples I-III of the written description.

(e). Claims 1, 16, 19, 21, and, 23 and claims dependent thereon are vague because the electron withdrawing groups recited as possible values for P are unclear in scope and not fully defined. Although applicants give examples of said electron withdrawing groups in the written description (page 9, line 25 to page 10, line 11), no teaching nor guidance (i.e. nature of testing and criteria) is provided to determine if a

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given group is electron withdrawing; therefore, it is unclear what groups fall within the applicants' intended scope.

(f). Claim 5 is indefinite because the use of the indefinite article "a" in "...a nitrile, a vinyl.." leaves open to speculation what particular nitrile or vinyl group(s) applicants intend to claim as part of their invention.

(g). Claims 1, 10, 17, 20, 22, and 24 are rejected for use of improper Markush groups. See MPEP 2173.05(h) for example of proper conventional or alternative Markush-type language.

(h). Claim 21 is vague because the term "biologically active thereof" is not defined. It appears that NO may be derived from several sources, but applicants do not point those out.

(i). Method claims 16-22 are rejected as being of indeterminate scope. It appears that mechanisms of action are recited rather than specific, intended uses thereby rendering the claims indefinite. With regard to claim 16, how many cells must be protected from oxidants-induced toxicity to satisfy the claim language? All? 98%? 95%?

The method claims are also unclear with regard to diseases claimed since the claim language embraces disorders not yet known to be associated with oxidant-induced toxicity or in ways not yet understood.

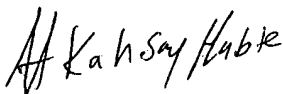
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Conclusion

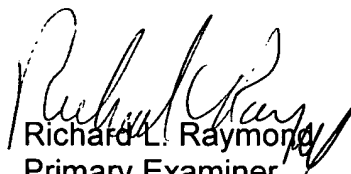
9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (703) 308-4717. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.



Kahsay Habte, Ph. D.
Examiner
Art Unit 1624



Richard L. Raymond
Primary Examiner
Art Unit 1624

KH
December 5, 2001